P24027 - MTT PAN TUMOR – ROUGH EDIT

EPISODE 1 V2 BREAK APART

MTT NHL & HL

Loretta Nastoupil, MD: Welcome to this *Med Table Talk*™ series on Lymphoma: The power of the community translating innovations into care in non-Hodgkin and Hodgkin lymphoma.

This is Part 1 of a 4-part series entitled, "Advances in Non-Hodgkin Lymphoma Care: Navigating New and Emerging Treatments." My name is Dr. Loretta Nastoupil from the University of Texas, MD Anderson Cancer Center, and I'd like to welcome my fellow colleagues to this program. Please introduce yourselves.

Ann LaCasce, MD: Hi, thank you for having me. My name is Dr. Ann LaCasce from Dana-Farber Cancer Institute in Boston.

Amitkumar Mehta, MD: Hi, thank you for having me. I'm Dr. Amitkumar Mehta. I am from the University of Alabama at Birmingham. I'm Director of Lymphoma and CAR T-cell program there.

Loretta Nastoupil, MD: I'm so happy to have you.

Non-Hodgkin lymphoma comprises much larger subclassification, and we first describe it, is this a B-cell lymphoma subtype or a T-cell lymphoma subtype? And T-cell lymphomas are quite rare.

So, most of what we're going to describe today is B-cell non-Hodgkin lymphoma, and the further subclassification is whether or not these are aggressive or indolent in nature. And oftentimes that is really a comparison between the two entities, meaning there are some times that indolent lymphoma can behave aggressively, whereas most of the time the aggressive lymphomas are going to need treatment rapidly because the disease kinetics are going to be quite different from what we're used to facing with indolent lymphomas.

Diffuse large B-cell lymphoma is actually our most common subtype of non-Hodgkin lymphoma, and that is comprised of about 17 different subclassifications. That may sometimes factor into how we approach this. We also use a number of clinical factors that help us risk-stratify patients.

So, we spent two decades trying to improve upon our standard approach, which was generally a CD20 antibody in combination with an anthracycline; and we knew that there were situations in which patients may not be well-served with that approach. So, oftentimes we use the IPI or International Prognostic Index to try and identify those at risk. If we could further subclassify the biology and identify high-risk subgroups such as high grade B-cell lymphoma or those with double-hit features, such as MYC rearrangement and BCL2, that may help us identify those that

we're nervous are not going to have the curative intent with standard approaches.

The NCCN Guidelines provide an overview for those in terms of how to approach this in frontline and in subsequent lines of therapy. And the focus of today's discussion is really what's changed in the treatment landscape for those in that second line or later space? We have known over the years that patients with aggressive non-Hodgkin lymphomas, such as diffuse large B-cell lymphoma, the aim of our frontline therapy is cure because for those patients who either progress or never achieve a complete remission, their outcomes can be quite poor.

And so making sure that we're aware of the treatment landscape as it emerges quickly for these rare tumor types will help address an unmet need of getting these newer effective therapies to where these patients are currently being treated.

But the disease itself is also aggressive, and now oftentimes three weeks things can change quite rapidly. And in providing the support patients and their caregivers need, given some of the toxicities associated with these therapies are quite unique and quite different from chemotherapy-based approaches in which people or, may have some experience and knowledge, so what are we talking about here? We're talking about CAR T-cell therapy and bispecific antibodies and how do they work?

So, these essentially are living therapies, meaning we're harnessing the patients' own T-cells to identify and eradicate tumor cells. And often time in that process, they're going to be activated, they're going to secrete cytokines. It's going to bring other immune cells into this environment that's going to leak, lead to leaky blood vessels which can lead to capillary leak-like syndromes with hypotension, hypoxia, third-spacing; and it's usually exaggerated beyond what would be a normal immune response, based off of the modifications that have been done to these cells.

Bispecific antibodies though can result in similar toxicity, particularly as it pertains to cytokine release syndrome, though it does not require the removal of patients' own T-cells. There's no viral vector, and so there's no modification of these cells. There's no extracellular receptor introduced, but it also can engage any T-cells and any CD20-expressing cells in the body. So tumor burden can also lead to quite significant symptoms in the first three weeks.

So first, most patients will have to be referred to a certified center that administers these therapies. And so understanding where the FDA approvals currently exist so that you could refer patient's office, an important part of this consideration. Once those patients are seen and they're deemed appropriate for CAR

T-cell therapy, they generally have to get or be approved financially to proceed because this is, essentially, a package deal, meaning we don't get approval just for one step of this process. Then we're monitoring these patients for disease symptoms for that again two- to four-week window where the manufacturing is occurring.

Once we get the green light that these cells meet the criteria to be released as a commercial product, patients return to that treating center. They undergo three days of lymphocyte-depleting chemo because these cells have been modified now, so we have to actually suppress their own immune system so that we can successfully infuse these cells back in. After about a two-day rest, they're infused. Some patients are infused in a hospital setting for close monitoring. Some are infused outpatient.

Generally, they're monitored for 28 days for cytokine release syndrome, ICANS or neurologic toxicity, as well as complications that may arise from the lymphocyte-depleting chemotherapy such as cytopenias and infection. And then day 28 we generally sit down with these patients; we go over how do they feel. Fortunately, most will fully recover from their acute toxicity. We generally do a response assessment at that timepoint, and

then we give them the guidance and counseling they may need for the next three to nine months.

There are other factors, so disease burden, inflammatory markers, pre-cell infusion such as LDH, ferritin, CRP, and again how quickly you can transition this patient from an outpatient setting into an inpatient setting where they may need therapies to mitigate these toxicities.

How do you navigate between CAR T and bispecifics, given we have indications for both in that third-line space?

Dr. LaCasce: I agree with what Loretta has said about trying to decide which patients might be appropriate for outpatient treatment. It's usually patients who are getting the 4-1BB like liso-cel, patients who don't have a huge amount of disease burden or comorbidities where it may be more difficult. You know, they may have more toxicity from the lympho-depleting chemo and that sort of thing.

I think you really need a very savvy family who feel comfortable with managing fevers and, you know, symptoms that will arise as things go forward. And I think there has to be very clear lines of communication. And I think point that you made about the ability to quickly admit patients is, is a barrier. You know, our hospitals are very, very full at the moment. I think this

is a nationwide problem, and getting patients to an emergency department and actually seen there and getting appropriate steroids and tocilizumab and quick therapy, I think, can be an issue. So, I think you have to have a good sense of what's going on at your center also in order to, to manage these patients as, in the outpatient setting.

Dr. Mehta: I totally agree with both of you. One other thing that, you know, I, I think education is a very important part, not only about the patient, but also the caregiver, as, as you rightfully said. And the other important aspect is developing what I call is an ecosystem for this CAR T-cell therapy. And that not just the center, but, you know, the patient, caregiver, even the emergency room; and many of the centers like ours, we have 24/7 infusion center, and that is usually covered by a nurse practitioner and a fellow. So, they're all part of this ecosystem that where the patient _____ is an outpatient, everybody's aware. And if something happens, they can intervene quickly.

But that is also critical that this ecosystem has an inpatient competent as, as you mentioned and, and/or the, because the patient needs to go in the hospital right away because at the end of the day, it's really an acute situation and can be turned around quickly with antidote like anti-IL-6 therapies.

Dr. Nastoupil: And so with those considerations, and now that we have bispecifics that are also available in that third line or later space, how are each of you navigating between these options? Assuming that you have a patient that's not had CAR in second line, and you're faced with sort of both options. So you've nicely illustrated some of the challenges with the toxicity with CAR T. We do see some overlap in terms of cytokine release syndrome, though very low rates of ICANS with the bispecific antibodies.

Dr. Mehta, I guess I'll start with you. How are you navigating this choice?

Dr. Mehta: Whenever they think about CRS and ICANS, they're always related to CAR T-cell therapy. And we know that with bispecific, the CRS is not as bad and usually happens in the first cycle. But, you know, in, in those situations, my first preference is still to consider CAR T-cell therapy if patient is eligible in both the second-line as well as third-line setting. I consider them as potentially curative. But if the patient by any means not eligible for CAR T-cell therapy, then in those situations I've consider bispecific.

Bispecific, I'll also use in post-CAR T setting. I would love to know your thoughts on, on, you know, kind of sequencing of this bispecific and CAR T-cell therapy.

Dr. Nastoupil: I have a similar approach. Sure. I consider patients for CAR T-cell therapy first if they've not had it, just because I have more experience and understanding about the durability. But there clearly are going to be patients where either they've progressed post-CAR or CAR's just not an option. And I do think that the bispecifics provide an off-the-shelf option that might be more readily available and attractive in a sense. And so I think it's good to have options to have both therapies available to us, and how do you navigate this?

Dr. LaCasce: I think we reach for a CAR T given the long-term data that we have that shows, you know, we have pretty good long-term, progression-free survival with the approved therapies. And we don't have as long follow-up with the bispecifics, so I think we need more data to know whether those are going to look as good as CAR T.

Yeah, I agree the community physicians, and it's not necessarily the oncologists. It's often that ecosystem that you talked about. You know, they don't have the ability to admit people quickly or to, you know, the familiarity isn't there. And I think, hopefully, that's going to improve over time; and there was, you know, there's some publications that have just come out, including one in *Blood* that really outlines how to manage the toxicity of bispecifics.

Fortunately, neurotoxicity is very, very rare; and most of the cytokine release is low grade, so it can be well-managed with steroids even. And I think we're going to get more and more experience with this. But I, I hope we can take this to the community setting because I know even our center in Boston, there are a lot of patients in the Northeast in rural areas where it is just not feasible for them to take time off, to get to the city, to be there. Even though we do have supports, there are financial supports with CAR T.

Sometimes, it's just too much; and I think that if we can work together with our community colleagues to be resources to help them administer these agents, I think once they start doing it, I think the anxiety around giving the bispecifics, and we've all seen that. I'm sure in your center when we started giving bispecifics, everybody's anxious because, you know, we're trying to do it as an outpatient. People are having fevers. Who has to go to the emergency department? But I think in pretty short order we're going to have much better algorithms to manage these folks predominately in the outpatient setting.

Dr. Mehta: One other argument that I want to make, and that has happened, you know, recently with a couple of patients that CAR T is more intense upfront. You know, like bispecific, some of

them, they continue to progression. Some of them, they were time-limited but still a year worth of therapy.

Well, when I discussed with my patients, one of the patients told me that, "Ha, so it's just, you know, one infusion and I'll be here for one month and that's, that's it. There is a 50% chance that this will be remission."

And that sometimes is very attractive, that they can bring in all their resources for first initial few weeks. But afterwards, if they're in remission, they don't need that compared to bispecific. It keeps on going for a while, depending on which product you're using.

Dr. LaCasce: Yeah, we're seeing a lot of infections in these bispecific antibody-treated patients who get a fair bit of steroids to mitigate the risk of CRS initially. And, you know, we've seen patients who have, you know, even rhinovirus that can persist for months; and patients are very symptomatic. They get neutropenic.

So, you know, I think that we think of the bispecifics as being necessarily a kinder, gentler approach. But that's, I think, again, we're learning about how to manage these patients and how long do we really need to treat them? Does it need to be indefinite? Probably not. So, I, I look forward to seeing more

data about the approval of these agents, how we're really going to use them in the clinic.

Dr. Nastoupil: I think you both ra-, raised, raised some really valid points. And I think the take-home for me is that as we get more clinical experience, we'll get better at navigating the sort of unique toxicities and balancing that out with the efficacy that, that we're accustomed to seeing now with the CAR Ts.

One other way to potentially navigate this is just to consider what are the current FDA approvals? Because there will likely be situations where you're also sequencing therapy.

And so we've been talking a lot about the CD19 auto CARs that were first approved late 2017 in that third line or later space. But we've seen migration of these therapies up into second line, at least with axi-cel and liso-cel based off of two large randomized, Phase III studies that were done in second line for those patients who relapsed within 12 months and were fit for intensive therapy because the control arm was platinum-based salvage chemotherapy and for responding patients, high-dose therapy autotransplant.

So, at least in our center, we've seen quite a bit of auto CD19 CAR utilization occurring in that second line. Has that been something you've seen at your centers as well?

Dr. LaCasce: Yeah, absolutely. I mean I don't remember the last time I've taken a patient actually to autologous stem cell transplant because I think the other issue is even if you have a patient who's relapsed after initial therapy, more than a year later, so they're no longer on label for second-line CAR, I want a complete remission before I'm going to take someone to an auto stem cell transplant because there you're completely relying on a high-dose chemotherapy approach. And with the patient isn't exquisitely chemo-sensitive, I would rather take patients to CAR T. So I think there's been a bit of a shift there where in the past we might have taken a partial remission patient and thought maybe we'll get lucky.

But now, you know, I think many of us, at least in our center, are reaching for CAR in that situation if they have a late recurrence and have really a complete remission to second-line therapy. Then yes, autotransplant is a very valuable tool, but it also is associated with significant toxicity and, you know, burden for patients and families.

Dr. Mehta: I think community has learned it very quickly, and they are referring the patients, especially primary refractory to the centers earlier.

Do, do I want to see those patients referred earlier? Do I want to see that myself or the ATC get involved earlier in the care? I'd definitely like to. So, many of, many of the double-hit, triple-hit, they actually call us right away. "Hey, this is aggressive patient. I want to start the treatment, but I'm very concerned that this patient might have highly refractory diffuse large B-cell lymphoma or aggressive B-cell lymphoma."

So, in those cases, it is important that we detect it early so that we can start the process of CAR T, you know, quicker. As you laid out, you know, it, it's a, it's a process. There are a lot of steps involved. There are a lot of people involved to get the patient in, collection, early insurance approval, admission planning, etc. So, I think the most important part, even though we are getting the referrals, I would love to see the referrals earlier than later.

Dr. LaCasce: The ZUMA-23 study is asking this question, can you take patients early to CAR, and they can get a cycle of therapy in the community. So, I think that's a really important study for these high-risk patients. As you said, it takes a bunch of

time to get them in your system and get the consult, so I, I think that's a really good suggestion.

Dr. Nastoupil: I absolutely agree with that, and so then I'm going to push back on both of you. We also have approvals outside of just large cell lymphoma, acknowledging that's our most common lymphoma subtype.

We do have approvals in follicular lymphoma in that third-line or later space and in relapsed mantle cell lymphoma. So how do you communicate to your referral center? Which are your base? Which patients would you like to be referred in with those less common subtypes? Ann, I'll start with you.

Dr. LaCasce: So, with follicular lymphoma, you know, I think we have an approved bispecific, mosunetuzumab. I think we'll probably have another agent. Epcoritamab is likely to be approved.

And honestly, I generally reach for those first because we will have CAR T later. The CAR T data looks very good, but the bispecific data looks very good as well. And I think it, the mosunetuzumab, in particular, is, is well-tolerated and one that, you know, we have started patients at our center and then transitioned patients back to the community to continue their therapy. So, there are a lot of clinical trials in that disease

that we have access to. So, we're sort of saving CAR in that disease until a little bit later.

For mantle cell, you know, I think once a patient is on a BTK inhibitor, we generally use it in third-line after BTK inhibitor, unless someone has had a BTK inhibitor upfront; and then I would think about using it in second line. So, I think if you have an aggressive mantle cell lymphoma, as soon as you see them failing frontline therapy and go on a BTK, I think, you know, setting up those referral patterns will be really helpful because those, some of those patients can get sick quickly and, and behave more like, you know, diffuse large B-cell lymphoma or aggressive lymphoma.

Dr. Mehta: Oh, I totally agree. I think follicular, the CAR T has fallen back to the later line of therapy with the newer therapies coming in, especially mosunetuzumab. Many of the patients are benefitting with that.

But I think, you know, in third-line setting or second-line even, we're getting referral for follicular lymphoma. So, we can plan it early. As you know there, follicular lymphoma is, most of the time, manageable. You know, unlike, we talked about aggressive B-cell or, as Ann mentioned, about B-MCL, which can explode on you. And you have very less time in that situation.

Compared with that, follicular is much, much better manageable. And whenever I communicate with my community doctors, we are still getting MCL referrals earlier because, you know, still a transplant is considered; and so we get the referrals earlier.

But I always warn that in MCL for those patients who have blastoid, pleomorphic, or TP53-mutated, those are the one which maybe one out of five patients would fall in that category. Two are ones that they may actually need CAR T earlier. And if you see that aggressive patient or high-mutated patient, make sure that you refer the patient earlier to ATC because that patient may need CAR T earlier rather than later.

Dr. Nastoupil: And great. And Ann already alluded to this. We have approvals for bispecifics, three currently, and anticipated broader labels coming soon.

You know, one key difference is also the CD20 targeting and the bispecifics versus CD19 that's currently in the FDA-approved autologous CAR T-cell domain. And so that does raise some interesting questions about sequencing of treatment, given you have a different antigen you're targeting. How does that factor into your treatment decisions? Amit?

Dr. Mehta: You know, Loretta, one of the things that I experienced lately, and I would love to know your experience on

that, that the bispecific, especially in DLBCL or aggressive B-cell lymphoma post-CAR T, I'm not seeing stellar responses ever expected. That actually pushed myself back a little bit. Maybe, you know, the sample size is not large enough; but I, I asked my colleagues around, and they're not stellar responses as we saw in the clinical trial. So, that, you know, keeps me thinking, well, there is something related to this T-cell health post-CAR T, and that's why these patients are not, are responding.

Also, in a post-CAR T setting, not all patients are similar. You know, those who relapse within the first three months or six months, they're usually very aggressive compared to those who relapse later. So, again, can I predict them beforehand? I'm not sure I'll, I'll be able to predict them before that this patient will be prime refractory.

But that actually, you know, one of the things that I'm thinking is whether I should use bispecific earlier than CAR T. That question always is in my, my mind. But you know, as we discussed, that long-term data of CAR T shows that there are potential cures in that. So that also is very attractive for me to go and use CAR T upfront. So, there is a dilemma there. And I'd love to know your thoughts on this situation.

Dr. Nastoupil: I think you bring some really good points up for discussion. I think the challenge with patients who qualify for clinical trials, they're always going to be sort of the best of our bad situation because they qualified for trial. They got to centers where they had access to trails. And so looking at those trials and understanding these subpopulations that are post-CAR T progression and being super excited about the efficacy, I think you have to dampen that down because I agree with you. In the real world, you're not going to have as good a result, most likely, because you're going to take sicker, frailer patients.

I hadn't thought about it though, and you bring up a good point about sequencing and could you utilize your bispecific earlier and try and optimize those patients by reducing the amount of disease and not hindering sort of that T-cell fitness with something like a bispecific? I think it's very intriguing.

We have seen data from the Europeans, so Gloria Iacoboni has done a really nice job looking through their registries and has looked at exposure to bispecific pre- and post-CAR and doesn't seem to see a negative impact of exposing these patients to bispecifics prior to CAR. So that's definitely reassuring.

And we're seeing the bispecifics quickly march into frontline in the trials that are under development. So, I think you're

right. In the future we'll probably have more patients that are exposed to bispecifics pre-CAR, and it'll be real interesting to see sort of how that impacts their outcome. Ann, any thoughts?

Dr. LaCasce: I think the other thing that it may be important to do in these settings is to rebiopsy patients and just make sure they still express CD20 because that, you know, you need to have, obviously, CD20 around in order to respond to a bispecific antibody.

And, you know, I think it's intriguing to, to think about what are those T-cells doing with the bispecifics; and I don't, I haven't seen that much data in terms of peripheral T-cell counts or, you know, what, what happens to those reserves? Are they getting all taken in as they are engaged into the, into the bispecific antibody? So, I'd love to see some more data about what the dynamics of the T-cell subsets are with these therapies.

Dr. Nastoupil: I think another important thing we have to acknowledge is that these are therapies that are currently most commonly used in academic centers or larger centers. How do we get this out into the community, acknowledging CAR T's probably never going to be a major consideration in a community practice? Bispecifics might, and so how do we reduce the barriers because these are clearly exciting therapies that are resulting in

durable remissions; and so we would want to ensure we have access to everyone, including those that can't uproot and, you know, relocate to that, our referral center for four to eight weeks. But what other things can we do to try and, again, reduce barriers to access? I'm curious to hear what your thoughts- Any sort of things you've applied in your population that you know is helpful?

Dr. LaCasce: I think getting early, early referrals and making sure that the local oncologists actually think to refer patients and not just assume that it's not going to be a feasible thing. You know, we can do some virtual visits with some of the New England states for our center, so sometimes even being able to talk someone through what it might look like and get the insurance approval underway before they actually have to come to the center, which is a very expensive proposition for many patients, and really trying to identify what resources are there to help support them once they arrive and then make sure that the local oncologist is okay with taking the patient back after the one-month mark. You know, these patients really want to get back home, and generally they do quite well at that point. But, you know, educating and being available if patients get, you know, have delayed cytopenias or hypogammaglobulinemia, or some of the complications that can arise.

So I, I think it's about these relationships between the academic centers and the referring docs and making sure that those are very open and often.

Dr. Mehta: They involve community doctors in decision-making because, you know, at the end of the day, majority of the cancer care happens in the community. So, those patients who are three hours away, four hours away from the center, they're very closely attached to their community doctor. So, I think how we can mobilize a resource so that, that we can utilize to increase the access of this, you know, fantastic drugs with excellent outcome.

So, I think that starts with the community doctor. So, educate, educate, and educate. And educate for the patient, educate to the community doctors, and how they can be a part of this decision-making, right? How can they feel comfortable picking up the phone, call us, the advanced treatment center, saying that, "Hey, I have a patient. The patient is good for bispecific or CAR T. I'm happy to work with you, send you this patient earlier, and I'll be part of the patient's care when they come out of the CAR T or bispecific. I'm happy to take over the bispecific treatment after their first cycle." So that kind of collaboration is the key.

The other important thing that has worked at our center is the patient navigation. So, you know, we see a significant number of minority patients referred to our center. And having the patient navigation program actually helps us a lot – understand them, understand their needs, how we can offer support, you know, local lodging. There are so many aspects of it, you know, that we learned that we can help support these patients to get this important, very important therapies.

Dr. Nastoupil: Yeah, great. I think you both highlight really key points but it all kind of boils down to communication. How can we improve that sort of open line for people that are curious about it, but they have some real concerns about whether or not their patient can uproot and move to those centers. And providing education also about how to manage the bispecific toxicity of CAR T. Really, it's just not something that's feasible for the patient, meaning they don't have a caregiver. They can't relocate. They can't even come for those first few weeks where you would need to be there for the CRS monitoring for bispecific.

So, I do think there's lots of opportunity, and I think the key is always going to be communication and being available to those community oncologists when they start that first patient on that

bispecific antibody. And then they have questions about how do you manage the CRS that just happened?

So, I think these are really important concepts, and I think now I'd like to put this into a case study so we can sort of put this in pr-, into practice. So, we have a 58-year-old male, initially diagnosed with diffuse large B-cell lymphoma about two years ago. Performance status is currently 2. Does have comorbidities, including hypertension, Type 2 diabetes, but it's well-controlled and has a history of osteoarthritis. He values maintaining his independence and quality of life. He's interested in treatment options that are going to offer that balance between efficacy and manageable side effects.

His initial treatment was R-CHOP, followed by radiation to consolidate the response. However, within nine months, he experiences worrisome symptoms; and imaging reveals new adenopathy, and a biopsy reveals that this is recurrent large cell lymphoma.

So, Ann, I'm going to start with you. How would you approach this patient?

Dr. LaCasce: So, this is a perfect patient for CAR T-cell therapy. He's within 12 months of his initial treatment. It, you know, he is having symptoms, so we know that burden of

disease correlates with symptoms in diffuse large B-cell lymphoma; and that also correlates with outcomes in CAR Ts. So, that's a little bit unfortunate, but you're going to want to try to get this patient going quickly to the referral center and get them, you know, consented and collected and then thinking about, you know, what is the optimal bridging therapy? If he's symptomatic, you're going to need to do something. This patient has not had polatuzumab, so I think that's a drug we often reach for. We don't know what subtype of diffuse large B-cell lymphoma he has, whether it's a germinal center or a nongerminal center, with the nongerminal center subtypes, you know, probably having better responses.

But I think, yeah, this is a great person for CAR, and I think, you know, the, Amit's discussion about the navigator is really critical. I think that really makes a difference. You know, having that person who can just call and check in, not even necessarily be responding to a question and just say, "Okay, here's what to expect, and here's what we're going to do for you." I'll try to get this patient in ASAP.

Dr. Nastoupil: Amit, any other thoughts?

Dr. Mehta: Yeah, I would also discuss CAR T-cell therapy with him. One thing that may need a clinic discussion when I see Mr. Smith in person is he values independence, and I've faced this,

especially CAR T. Remember, those patients cannot drive for two months. And I've seen many Mr. Smiths. That actually is a critical point for them, that I will be dependent on somebody for, for, for driving and mobility.

In that particular case, I would support that, that in the beginning. This is a one-time treatment, and then afterwards you'll be practically independent compared to any other therapy, even if you take, you know, CD19-directed therapy with lenalidomide or any other multiple infusions, right? So, this is a one-time treatment upfront that he'll, he'll have to gather his resources to support him through. But then after we'll, afterwards he will have an independent life.

Dr. Nastoupil: I agree. I cannot envision another therapy that's not as likely to give him what he's hoping for, which is independence and having sort of his normal life as possible. I do think the advantages with CAR is that it is upfront sort of intensity, but generally, most people have full resolution of their side effects within the first 30 days.

Infection, I counsel patients on after the first 30 days. And you can sort of tailor your choice of CAR to try and mitigate some of those concerns. I think with an ECOG performance status of 2, this is somebody I might consider liso-cel over axi-cel

for that reason. But I, I do agree that CAR T is, by far and away in my opinion, the best choice in this given situation.

So, now I'm going to ask you in your perfect world, what do you think we could do to try and address some of the limitations with the current therapies we have and also getting that out to a broader population? And Ann, I'll start with you.

Dr. LaCasce: Really making sure that we have open communication with our referring physicians to make sure that they feel comfortable sending patients early and for us to be available to them when patients go back home, particularly with CAR T or, you know, I think we hopefully, in the near future, will be able to roll out bispecifics in the community. I think it's very feasible and safe, but we need to be there to support people because these therapies were all developed in big academic centers, so we've had lots of experience, and we've been able to get comfortable with the toxicity. So, I think it's time for us to share that expertise and support to the communities because not everybody, even with support and with financial health, can make it to a big academic center.

Dr. Mehta: I think about CAR T, and CAR T's done, right? I don't have, I don't have to fight with the insurance, right? The patient, it can be collected right away. There are no out-of-spec products, right? I mean all of those challenges that we

face, and minimal CRS and ICANS and as, as we discussed about Mr. Smith who can be back to his independent world right away within a month.

Dr. Nastoupil: I agree. I think there's really nothing quite else like CAR T in the relapsed/refractory setting, particularly for those patients who relapse early. Would I like to see improvements? Absolutely. I'd rat-, I'd really like to see an improvement in flow of the patient from the community center to the academic center and back. I'd like to see much less resource utilization requirements for delivery of the CAR, collecting the cells, awaiting the manufacturing, the bridging. And I would love to see a world where we don't have to consider the post-CAR failure space, which is actually becoming a little bit harder, in my opinion, to really manage.

But I do think that CAR Ts offer really effective strategy that can be well-tolerated, and I'm very optimistic about the bispecifics and that they provide another interesting and effective strategy that doesn't require the manufacturing of a live product. So, I'm just really excited for, you know, what the next five years will lead to.

Thank you, Dr. LaCasce and Dr. Mehta, and thank you for joining for Part 1 in this series. Stay tuned for Part 2 where we will discuss, "Making the Right Selection: Expert Guidance on

Treatment Sequencing of T-cell Mediated Therapies." Part 3 where we will discuss, "The Power of the Community: Translating Innovations Into Care in Non-Hodgkin and Hodgkin Lymphoma." And our final part where we discuss, "Checkpoint Conversations: Integrating Immune Checkpoint Inhibitors in Hodgkin Lymphoma."

For additional resources, please see the activity website. To claim credit, please complete the post-assessment questions and evaluation. Take care.

END OF EPISODE 1